Epilepsy & Behavior 37 (2014) 270–275

Contents lists available at ScienceDirect

Epilepsy & Behavior

journal homepage: www.elsevier.com/locate/yebeh

Effect of positive airway pressure therapy on seizure control in patients with epilepsy and obstructive sleep apnea

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ARTICLE INFO

Article history:
Received 15 March 2014
Revised 18 June 2014
Accepted 7 July 2014
Available online 12 August 2014

Keywords:
Obstructive sleep apnea
Positive airway pressure therapy
Polysomnography
Seizure outcome
Epilepsy
Comorbidities

ABSTRACT

Previous studies suggest that treatment for obstructive sleep apnea (OSA) in patients with epilepsy can improve seizure control. We investigated the effect of positive airway pressure (PAP) therapy on seizures in adults with epilepsy referred to the Cleveland Clinic for polysomnography (PSG) from 1997 to 2010. Seizure outcome at baseline and 1 year later was compared in patients with no OSA (apnea–hypopnea index [AHI] <5), patients with PAP-treated OSA, and patients with untreated OSA. One hundred thirty-two subjects (age: 40.2 ± 13 (18–76) years, 65.4% female) were included. Seventy-six (57.6%) subjects had OSA; of these, 43 (56.6%) were on PAP therapy, and 33 (43.4%) were not on PAP therapy (either PAP-intolerant or refused therapy). Of the group with PAP-treated OSA, 83.7% were adherent (use ≥4 h/night at least 5 nights/week). The percentage of subjects with ≥50% seizure reduction and the mean percentage of seizure reduction were significantly greater in the group with PAP-treated OSA (73.9%; 58.5%) than in subjects with untreated OSA (14.3%; 17.0%). There were significantly more subjects with successful outcomes (with ≥50% seizure reduction or seizure-free at both baseline and follow-up) in the group with PAP-treated OSA (83.7%) than in the groups with no OSA (53.6%) and untreated OSA (39.4%). After adjusting for age, gender, body mass index, AHI, and epilepsy duration, we found that the odds of successful outcomes in subjects in the group with PAP-treated OSA were 9.9 and 3.91 times those of the groups with untreated OSA and no OSA, respectively. The group with PAP-treated OSA had 32.3 times the odds of having a ≥50% seizure reduction compared with the group with untreated OSA and 6.13 times compared with the group with no OSA. Positive airway pressure therapy appears to produce beneficial effects on seizures in adult patients with epilepsy and OSA.

1. Introduction

Obstructive sleep apnea (OSA) is a highly prevalent disorder, affecting 24% of men and 9% of women in the U.S. based on studies published in the 1990s when obesity rates were lower than current estimates [1]. The prevalence of OSA was 33% among 39 adults with pharmacoresistant focal epilepsy [2] and 30% among 130 adults with epilepsy unselected for sleep disorder complaints, including 16% with moderate-to-severe disease [3], rates that markedly exceed general population estimates. Previously, most retrospective case series have shown that treatment for OSA with positive airway pressure (PAP) therapy or upper airway surgery improved seizure control in some patients with OSA and epilepsy [4–12]. We aimed to investigate the effect of PAP therapy on seizure control by comparing seizure outcomes in adults with epilepsy with PAP-treated OSA, patients with untreated OSA, and patients with no OSA.

2. Methods

This study was approved by the Cleveland Clinic Institutional Review Board, and subjects provided written informed consent prior to the completion of study procedures. We undertook a retrospective review of clinical and polysomnographic data of adults with epilepsy who underwent polysomnography (PSG) at the Cleveland Clinic from 1997 to 2010 either as part of a research study or for the clinical evaluation of OSA. Research subjects provided written informed consent prior to the completion of study procedures. Inclusion criteria included the following: 1) age ≥ 18 years, 2) confirmed epilepsy based on clinical history and EEG or MRI, and 3) seizure frequency data documented in a standardized manner (per month for each seizure type) in the electronic medical record (EMR) over the 6 months prior to PSG and at a clinical visit 6–12 months later.

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http://dx.doi.org/10.1016/j.yebeh.2014.07.005
1525-5050/

2.1. Study procedures

2.1.1. Clinical data collection

Clinical data including demographics (age, gender, and body mass index [BMI]) and epilepsy characteristics (epilepsy classification, seizure frequency, and type and dosage of antiepileptic drug [AED] therapy) were obtained through EMR review. Epilepsy was classified as focal, generalized (presumed genetic and symptomatic), or undetermined. Seizures were classified as generalized motor (tonic, clonic, myoclonic, or tonic–clonic) or nonconvulsive (focal or absence/dialeptic), excluding auras. Mean monthly seizure frequency was determined over 6 months prior to baseline and at follow-up 6–12 months after PSG. Type and total daily dose of AEDs were obtained at baseline and follow-up, excluding those taken as needed for prolonged seizures or seizure clusters. A standardized variable of the amount of AED taken daily was determined using the defined daily dose (DDD), a measure based on the assumed average daily dose in its main indication for adults assigned by the World Health Organization [13,14]. The prescribed daily dose (PDD)/DDD ratio was calculated and summed over all drugs for each subject. Standardized AED values >1 indicate dose regimens higher than the average.

2.1.2. Polysomnography

Subjects underwent PSG with 6- to 18-channel EEG recording, right and left electrooculogram, submental and bilateral tibialis anterior electromyography, airflow using nasal pressure transducer and naso-oral thermistor, effort using thoracoabdominal piezoelectric belts, snoring, body position, pulse oximetry, and electrocardiogram. Sleep staging and event scoring were performed according to published guidelines [15]. Apnea was defined as a ≥90% decrement in airflow for ≥10 s. Hypopnea was defined as a ≥50% reduction in the nasal pressure transducer signal lasting ≥10 s resulting in an arousal or ≥3% desaturation (alternate definition) as was customary in our laboratory. Obstructive sleep apnea was diagnosed by an AHI ≥ 5; subjects with AHI < 5 were classified as having no OSA. At the time of PSG, subjects completed the Epworth Sleepiness Scale (ESS), an 8-item questionnaire that measures one's propensity to fall asleep in 8 everyday situations [16]. An ESS score ≥10 is considered indicative of excessive daytime sleepiness.

2.1.3. PAP titration and adherence

Subjects with OSA had an overnight PAP titration to identify optimal pressure with the exception of three subjects who underwent autotitration (AutoPAP) in the home. The quality of titrations was graded as optimal (AHI < 5 for at least 15 min including supine REM sleep), adequate (AHI not normalized but reduced by 75% from baseline or absence of supine REM sleep at effective pressure), or suboptimal (not meeting other criteria) based on published criteria [17]. Subjects with OSA were educated about the adverse consequences of OSA and treatment options and then offered PAP therapy. Subjects with OSA were subdivided into PAP-treated OSA and untreated OSA (PAP-intolerant or refused treatment) for analysis. Positive airway pressure adherence was ascertained at the follow-up visit and defined as full (≥4 h/night ≥70% of nights) or partial (lesser amounts of use) based on self-report and adherent (≥4 h/night on average) or nonadherent (<4 h/night on average) based on machine download when available.

2.1.4. Seizure outcome assessment

Mean and median monthly seizure frequency were determined over the 6-month period prior to PSG and at a clinical visit 6–12 months later. The primary seizure outcome was percent of subjects with ≥50% seizure reduction (responder rate) for subjects not seizure-free at baseline. Responder rate, percent change from baseline to follow-up (for all subjects), and percent of subjects with successful outcomes (≥50% total seizure reduction in patients not seizure-free at baseline or continued seizure freedom in those seizure-free at baseline) were calculated.

2.2. Statistical analysis

The data were presented as mean, standard deviation (SD), and percentiles of interest for continuous variables and frequencies and percentages for categorical variables. Median rather than mean data were used for seizure outcome tests, given that the data were not normally distributed. We compared demographics, epilepsy-related variables, ESS scores, PSG variables, and seizure outcome between the groups with PAP-treated OSA, untreated OSA, and no OSA. Pearson's Chi-squared test and Fisher's exact test were used to compare categorical factors, while Kruskal–Wallis tests were used for continuous measures. For comparisons of the three study groups, when significant overall tests were observed, Bonferroni-adjusted Wilcoxon rank sum tests were used to identify differences among the 3 groups for each measure while controlling the overall significance level at 0.05. In these comparisons, a p-value < 0.017 (0.05/3) was considered statistically significant. While we used this criterion, we also chose to present all p-values unadjusted, which allows the reader to use their preferred significance level. Logistic regression models were used to compare groups on successful outcome and responder rate, adjusting for age, gender, BMI, AHI, and epilepsy duration. Nonparametric restricted cubic splines were used to flexibly fit the relationship between continuous measures and the response. In all cases, diagnostic tests indicated that the nonlinear fits of these covariates were unnecessary, so linear fits were used. The Hosmer–Lemeshow test was used to evaluate goodness of fit for the logistic models. Analyses were performed using R software (version 2.15; Vienna, Austria).

3. Results

One hundred thirty-two subjects including 85 (65.4%) females having a mean age of 40.2 ± 13 years (18–76) were included. Seventy-six (57.6%) subjects had OSA. Of these, 43 (56.6%) were on PAP therapy (40 CPAP and 3 AutoPAP) and 33 (43.4%) were not on PAP therapy. With the exclusion of subjects seizure-free at baseline, our sample included 23 subjects with PAP-treated OSA, 21 subjects with untreated OSA, and 37 subjects with no OSA.

Overall demographic and epilepsy-related variables by group are summarized in Table 1 and for the subset of subjects not seizure-free at baseline in Supplemental Table 1. Overall results and among subjects not seizure-free at baseline were similar with the exception that a difference in epilepsy duration was observed in the overall sample, while no difference between groups was found among the subset not seizure-free at baseline. In addition, among seizure-free patients, a significant difference in baseline generalized motor seizures was observed. The majority of subjects (71.2%) had focal epilepsy. Mean monthly seizure frequency for total, focal/dialeptic, and generalized motor seizures was 3.9, 2.5, and 1.4, respectively, and did not differ between groups in the overall sample. Antiepileptic drug type or dosage change between baseline and follow-up was made in 26.5% of the subjects. However, the standardized AED dose change was minimal and not significantly different between groups. No subjects underwent epilepsy surgery during the follow-up period. Subjects without OSA were significantly younger, more likely to be female, and had lower BMIs compared with the two groups with OSA. Age, gender, and BMI did not differ between the groups with PAP-treated OSA and untreated OSA.

Polysomnographic data are shown in Table 2. The mean AHI for all subjects was 13.0 ± 16.6 events/h. As expected, subjects without OSA had lower overall supine and REM AHI and higher SpO_2 nadir compared with the group with OSA. The median [P25, P75] AHI in the PAP-treated OSA group was significantly higher than that in the group with untreated OSA. Positive airway pressure data for the 43 subjects with PAP-treated OSA are shown in Table 3. The majority of subjects with PAP-treated OSA were fully adherent to PAP therapy based on self-report. In the subset of fourteen subjects with PAP-treated OSA with available objective adherence data, all those reporting full adherence met the objective

Table 1
Baseline characteristics in the groups with PAP-treated OSA, untreated OSA, and no OSA.

	PAP-treated OSA		Untreated OSA		No OSA		p-Value
	N	Statistics	N	Statistics	N	Statistics	
Age, year[a]	43	45 [35, 51]	33	49 [39, 56]	56	31.5 [25.8, 38]	<0.001
BMI, kg/m^{2}[b]	43	33.7 [27.5, 39.6]	33	29.5 [27.6, 35.7]	56	25.1 [22.9, 30]	<0.001
Sex, % female[c]	20	46.5	19	57.6	46	82.1	<0.001[C]
Epilepsy type, %							0.76[F]
Focal	31	72.1	24	72.7	39	69.6	
Generalized	10	23.26	6	18.18	15	26.79	
Unknown	2	4.7	3	9.1	2	3.6	
Total SZ/mo							0.96
Mean ± SD	43	4.66 ± 9.86	33	4.61 ± 8.97	56	2.83 ± 6.13	
Median [P25, P75]	43	0.17 [0, 4.25]	33	0.3 [0, 4]	56	0.23 [0, 2]	
Focal/dialeptic							0.50
Mean ± SD	43	3.5 ± 8.73	33	2.74 ± 6.13	56	1.55 ± 5.01	
Median [P25, P75]	43	0 [0, 1.75]	33	0 [0, 1]	56	0 [0, 0.37]	
Generalized motor							0.14
Mean ± SD	43	1.16 ± 2.1	33	1.87 ± 7.26	56	1.28 ± 3.27	
Median [P25, P75]	43	0 [0, 1.5]	33	0 [0, 0]	56	0 [0, 0.29]	
SZ-free, %	20	46.5	12	36.4	19	33.9	0.42[C]
AED change, %[d]	11	25.6	13	39.4	11	19.6	0.13[F]
STD dose							
Baseline	43	1.7 [1.33, 2.88]	33	2 [1, 3.2]	56	1.55 [1, 2.67]	0.73
Follow-up	43	1.7 [1.3, 3.11]	33	2 [1, 3.67]	56	1.67 [1.16, 2.92]	0.85
Change	43	0 [0, 0]	33	0 [0, 0.2]	56	0 [0, 0]	0.82
Epilepsy duration, year[e]	40	24.5 [11.5, 32.25]	32	23.5 [16.75, 39]	48	16.5 [7, 24]	0.043
Follow-up, months	43	9.7 [7.3, 11.4]	33	10.3 [8.6, 11.7]	48	11.0 [8.4, 12.9]	0.37

Median [P25, P75] for continuous variables unless otherwise indicated; percentage for categorical variables.
Abbreviations: SZ = seizure; STD dose = AED standardized dose.
Kruskal–Wallis rank sum test unless C (Pearson's chi-squared test) or F (Fisher's exact test for count data).
[a] Using a 0.017 significance level; the group with no OSA differs from the other two groups (PAP-treated OSA ($p < 0.001$) vs. untreated OSA ($p = 0.23$)).
[b] The group with no OSA differs from the other two groups (PAP-treated OSA ($p < 0.001$) vs. untreated OSA ($p = 0.17$)).
[c] The groups with PAP-treated OSA and no OSA differ ($p < 0.001$); PAP-treated OSA vs. untreated OSA ($p = 0.47$); untreated OSA vs. no OSA ($p = 0.023$).
[d] AED type or dose change.
[e] No significant differences in multiple comparisons (PAP-treated OSA vs. untreated OSA ($p = 0.85$); PAP-treated OSA vs. no OSA ($p = 0.029$); untreated OSA vs. no OSA ($p = 0.042$)).

criteria for adherence, and those without full adherence failed to meet this standard.

Seizure outcome data are shown in Table 4 for all subjects and in Supplemental Table 2 for the subset of subjects without AED change in drug or dosage. While there was no significant difference in monthly seizure frequency or percent seizure-free subjects at baseline between groups, seizure reductions were greater in the group with PAP-treated OSA compared with the others, particularly between the group with PAP-treated OSA and the group with untreated OSA, where the mean percentage of seizure reduction was 58.5% and −17.0%, respectively. There were significantly more subjects with successful outcomes (≥50% reduction or seizure-free at both baseline and follow-up) in the group with PAP-treated OSA (83.7%) than in the groups with no OSA (53.6%) and untreated OSA (39.4%). No change in seizure outcome was observed among subjects who were seizure-free at baseline. Among subjects not seizure-free at baseline, the responder rate was significantly greater in the group with PAP-treated OSA (73.9%) than in the group with untreated OSA (14.3%), and successful outcomes were significantly more likely in the group with PAP-treated OSA (83.7%) than in the groups with untreated OSA (39.4%) and no OSA (53.6%). Furthermore, 28% of the subjects who were not seizure-free at baseline became seizure-free at follow-up, including 35% of the

Table 2
Polysomnographic data in the groups with PAP-treated OSA, untreated OSA, and no OSA.

	Total	PAP-treated OSA		Untreated OSA		No OSA		p-Value
		N	Statistics	N	Statistics	N	Statistics	
AHI	132	43	18 [12.9, 32.4]	33	11.9 [8.6, 18]	56	0.65 [0.2, 1.6]	<0.001[a]
AHI supine	115	39	25 [15.2, 44.5]	30	17.25 [8.56, 27.9]	46	0.45 [0, 2]	<0.001[b]
AHI REM	110	38	32.8 [23.0, 45.4]	28	19.4 [10.1, 29.0]	44	1.05 [0, 2.1]	<0.001[c]
SpO_2 nadir	121	43	85 [79.5, 87.5]	31	87 [86, 90]	47	91 [87, 93]	<0.001[d]
TST < 90%	115	41	1.7 [0.2, 9.7]	31	0.5 [0, 2.9]	43	0 [0, 0.35]	<0.001[e]
PLMI	132	43	0.7 [0, 4.7]	33	0 [0, 2.4]	56	0 [0, 0.72]	0.074
ESS	125	42	8 [5, 11.8]	30	7.5 [6, 11.8]	53	7 [4,10]	0.16
ESS ≥ 10	125	15	35.7%	13	43.3%	15	28.3%	0.37

Median [P25, P75] for continuous variables, otherwise percentage.
Abbreviations: AHI = apnea–hypopnea index; TST < 90% = total sleep time with $SpO_2 < 90\%$; PLMI = periodic limb movement index; ESS = Epworth Sleepiness Scale.
Kruskal–Wallis rank sum test.
[a] The group with no OSA differs from the other two groups ($p < 0.001$), and the groups with PAP-treated OSA and untreated OSA differ ($p = 0.004$).
[b] The group with no OSA differs from the other two groups ($p < 0.001$), and the groups with PAP-treated OSA and untreated OSA do not differ ($p = 0.021$).
[c] The group with no OSA differs from the other two groups ($p < 0.001$), and the groups with PAP-treated OSA and untreated OSA differ ($p = 0.007$).
[d] The group with no OSA differs from the other two groups ($p < 0.001$ vs. PAP-treated OSA and $p = 0.001$ vs. untreated OSA), and the groups with PAP-treated OSA and untreated OSA do not differ ($p = 0.029$).
[e] The group with no OSA differs from the other two groups ($p < 0.001$ vs. PAP-treated OSA and $p = 0.001$ vs. untreated OSA), and the groups with PAP-treated OSA and untreated OSA do not differ ($p = 0.069$).

Table 3
PAP data in PAP-treated subjects.

Variable (N = 43)	
Mode	
CPAP	40 (93.0)
AutoPAP	3 (7.0)
Titration grade	
Optimal	35 (87.5)
Adequate	5 (12.5)
Suboptimal	0 (0)
CPAP pressure, cmH_2O	9.5 ± 3.0
Adherence	
Full	36 (83.7)
Partial	7 (16.3)
Use, h/night	6.63 ± 1.39
Use, nights/week	6.59 ± 1.02

N (%) for categorical variables, otherwise mean ± SD.

subjects with PAP-treated OSA, 10% with untreated OSA, and 35% with no OSA. Seizure outcomes were not significantly different between subjects with mild OSA and those with moderate-to-severe OSA or between those with focal epilepsy and those with generalized epilepsy. The percentage of subjects with successful outcomes was similar in subjects with PAP-treated OSA with full and partial adherence. Of the 7 subjects with partial adherence, 6 were seizure-free at baseline. There was no significant difference between adherence groups on seizure change, and the number of partially adherent subjects with seizures at baseline precluded further comparisons of this subgroup. Results comparing groups among subjects without AED change were similar to the overall results, except for nonsignificant differences seen at follow-up in overall seizure change.

Results of multivariable models adjusting for age, gender, BMI, AHI, and epilepsy duration revealed odds ratios (95% confidence interval [CI]) of achieving a ≥50% seizure reduction for subjects with PAP-treated OSA relative to those with untreated OSA and no OSA of 32.3 (5.92, 266.3; $p < 0.001$) and 6.13 (0.95, 45.0; $p = 0.056$), respectively. The odds ratios for achieving a successful outcome for subjects with PAP-treated OSA relative to the groups with untreated OSA and no OSA were 9.90 (3.13, 35.6; $p < 0.001$) and 3.91 (0.98, 17.5; $p = 0.061$), respectively. None of the adjusting factors were statistically significant.

4. Discussion

Obstructive sleep apnea is a highly prevalent disorder characterized by recurrent sleep-related respiratory events associated with arousal or oxygen desaturation, resulting in a state of chronic sleep deprivation and a host of medical and psychosocial comorbidities [18]. While weight loss and lifestyle modification are integral components of the treatment plan in OSA, PAP therapy is the first-line treatment for moderate-to-severe disease. Positive airway pressure therapy eliminates respiratory events, arousals, and oxygen desaturations, thereby reducing daytime sleepiness, depressed mood, cognitive impairment, and blood pressure and enhancing metabolic and cardiovascular outcomes [19].

Table 4
Seizure outcome in the groups with PAP-treated OSA, untreated OSA, and no OSA at follow-up.

	PAP-treated OSA		Untreated OSA		No OSA		p-Value
	N	Statistics	N	Statistics	N	Statistics	
Total SZ/mo							0.11
Mean ± SD	43	1.46 ± 2.47	33	4.97 ± 8.96	56	2.69 ± 6.37	
Median [P25, P75]	43	0 [0, 2.25]	33	0.17 [0, 7]	56	0.04 [0, 1.62]	
Focal/dialeptic							0.060
Mean ± SD	43	1.05 ± 2.19	33	3.08 ± 6.17	56	1.53 ± 5	
Median [P25, P75]	43	0 [0, 0.5]	33	0.17 [0, 4]	56	0 [0, 0.17]	
Generalized motor							0.66
Mean ± SD	43	0.41 ± 1.01	33	1.89 ± 7.26	56	1.17 ± 3.61	
Median [P25, P75]	43	0 [0, 0]	33	0 [0, 0]	56	0 [0, 0]	
SZ change[a]							0.004
Mean ± SD	43	−3.2 ± 8.46	33	0.37 ± 1.08	56	−0.14 ± 1.81	
Median [P25, P75]	43	0 [−2, 0]	33	0 [0, 0]	56	0 [−0.29, 0]	
SZ change – SF							0.40
Mean ± SD	20	0.10 ± 0.45	12	0.17 ± 0.44	19	0.04 ± 0.09	
Median [P25, P75]	20	0 [0, 0]	12	0 [0, 0]	19	0 [0, 0]	
SZ change – NSF[b]							<0.001
Mean ± SD	23	−6.07 ± 10.86	21	0.48 ± 1.31	37	−0.23 ± 2.23	
Median [P25, P75]	23	−2 [−2.75, −0.17]	21	0 [0, 0]	37	−0.17 [−0.7, 0]	
% decrease[c]							0.004
Mean ± SD	23	58.52 ± 50.36	21	−16.97 ± 120.42	37	18.5 ± 134.17	
Median [P25, P75]	23	72.7 [45.8, 100]	21	0 [0, 0]	37	35 [0, 100]	
Responder, %[d]							<0.001[C]
Yes	17	73.91	3	14.29	15	40.54	
No	6	26.09	18	85.71	22	59.46	
Successful outcome[e]							<0.001[C]
Yes	36	83.72	13	39.39	30	53.57	
No	7	16.28	20	60.61	26	46.43	

Mean ± SD, median [P25, P75] for continuous variables, otherwise percentage.
Abbreviations: SZ = seizure; mo = month; SF = seizure-free at baseline; NSF = not seizure-free at baseline; responder ≥ 50% seizure reduction; C = Pearson's chi-squared test.
Kruskal–Wallis rank sum test unless otherwise indicated.

[a] Using a 0.017 significance level, the group with PAP-treated OSA differs from the group with untreated OSA ($p < 0.001$); the groups with PAP-treated OSA and no OSA do not differ ($p = 0.057$); the groups with untreated OSA and no OSA do not differ ($p = 0.060$).

[b] The group with PAP-Treated OSA differs from the other two groups ($p < 0.001$ vs. untreated OSA and $p = 0.002$ vs. no OSA); the groups with untreated OSA and no OSA do not differ ($p = 0.020$).

[c] The group with PAP-treated OSA differs from the group with untreated OSA ($p < 0.001$); the groups with PAP-treated OSA and no OSA do not differ ($p = 0.17$); the groups with untreated OSA and no OSA do not differ ($p = 0.046$).

[d] The groups with PAP-treated OSA and untreated OSA differ ($p < 0.001$). The groups with PAP-treated OSA and no OSA do not differ ($p = 0.024$); the groups with untreated OSA and no OSA do not differ ($p = 0.075$).

[e] The groups with PAP-treated OSA and untreated OSA differ ($p < 0.001$); the groups with PAP-treated OSA and no OSA differ ($p = 0.003$); the groups with untreated OSA and no OSA do not differ ($p = 0.28$).

In addition to these beneficial effects of PAP, our study provides further evidence that PAP therapy can improve seizure control in people with epilepsy. Adults with epilepsy and OSA had significantly better seizure outcomes when treated with PAP on several measures including responder rate, percent seizure reduction, and successful outcomes (≥50% total seizure reduction in patients not seizure-free at baseline or continued seizure freedom in those seizure-free at baseline) compared with similar patients with untreated OSA or no OSA.

Despite its retrospective nature, our study extends prior observations of the impact of PAP therapy on seizure control and is strengthened by the following design features: 1) standardized format of seizure frequency data recorded in the EMR in a large sample, 2) incorporation of a standardized AED dose variable representing a subject's drug burden as a covariate, and 3) use of a comparator group without OSA having similar epilepsy-related characteristics, though with a demographic profile (younger, more females, lower BMI) suggesting a lower risk of OSA.

While the groups with PAP-treated OSA and untreated OSA were similar in terms of demographics, the group with PAP-treated OSA had a higher AHI, suggesting more severe OSA. This difference might have been expected to result in less seizure improvement over time, further emphasizing the positive impact of PAP therapy on seizures. Importantly, PAP therapy was recommended in all subjects with OSA. Additionally, all subjects with OSA were provided with information on conservative therapies for OSA including weight loss, sleeping off supine, and treatment for nasal congestion.

Our study has several limitations. In the group with PAP-treated OSA, PAP adherence was determined based on self-report. This was necessary since objective download capability was not a feature of all PAP machines during the earlier years of our study, and, when available, objective adherence data were not stored in the EMR in a standardized manner as is done currently. However, we found a strong correlation between objective PAP use and self-reported use in the subset with objective data. Additionally, we included subjects seizure-free at baseline to address the natural variations in seizures over time, reflective of a general epilepsy practice. While we evaluated outcomes in all subjects and then separately by seizure-free status at baseline, the number of subjects not seizure-free at baseline (23 with PAP-treated OSA and 21 with untreated OSA) is not larger than that in prior reports. Finally, the extent to which subjects implemented conservative therapies for OSA and the impact on such implementation on seizure outcomes are unknown, given our retrospective design.

Treatment for OSA with PAP therapy has been shown to produce beneficial effects on seizure control in several retrospective case series [4–6, 8–11]. The only randomized controlled trial (a pilot study exploring feasibility of treating OSA in pharmacoresistant focal epilepsy) found a ≥50% seizure reduction in 6 (28%) of 22 subjects in the therapeutic PAP group as compared with 2 (15%) of 13 in the sham PAP group ($p = 0.40$); four subjects treated with therapeutic PAP and one treated with sham became seizure-free [8]. However, the trial was not powered to measure the impact of PAP therapy on seizure control.

Shorter follow-up periods, concomitant AED changes, and uncertainties related to adherence measurements and therapeutic pressure confirmation confound earlier studies. The largest and most recent study involving 28 PAP-adherent and 13 non-adherent patients found that noncompliance with CPAP use increased the risk of lack of seizure freedom by about 1.5-fold with 57% of PAP-adherent patients seizure-free after 6 months of therapy in the absence of AED adjustments [12]. In another study, PAP therapy produced a reduction in spike rate in six adults with epilepsy, suggesting that treatment for sleep disorders may reduce epileptogenicity [20]. While we found no significant difference in follow-up duration between groups and follow-up duration was longer than that in prior studies, it remains unknown whether small differences in follow-up between the groups with PAP-treated OSA and untreated OSA may have impacted our results. Prospective, randomized studies are needed to overcome these limitations.

After adjusting for important covariates, we found that subjects with untreated OSA had significantly lower odds of achieving a successful outcome or a ≥50% seizure reduction compared with subjects with PAP-treated OSA despite having less severe OSA, although the confidence intervals are wide. Because standardized AED dose was similar between groups at baseline and follow-up, alterations in AED therapy are not likely to have contributed significantly to these findings. Importantly, subjects with mild OSA obtained the same magnitude of benefit from PAP use as those with moderate-to-severe disease. Seizure outcomes were also similar between patients with focal epilepsy and those with generalized epilepsy and did not differ by baseline seizure frequency, underscoring the importance of early diagnosis and treatment for OSA in patients with epilepsy regardless of epilepsy type or seizure status.

Given the high prevalence of OSA in adults with epilepsy and the growing evidence that PAP therapy reduces seizures, we believe that routine clinical screening for OSA is warranted and that PAP therapy should be considered in all PSG positive cases. Notably, results of the ESS were similar between groups with means in the normal range, suggesting that this scale may not assist in the identification of OSA among adults with epilepsy. Considering all OSA subjects combined, we found that PAP adherence was only 56.6%, in keeping with general population estimates of 48–83% [21]. Despite these diagnostic and therapeutic challenges, given that seizures are incompletely controlled in 30–40% of people with epilepsy, the need for a better understanding of the impact of sleep comorbidities in epilepsy is compelling [22]. Our study offers further evidence that PAP therapy produces beneficial effects on seizures in adults with epilepsy independent of epilepsy type or severity and regardless of the severity of OSA. Prospective, randomized trials are required to provide definitive evidence of the beneficial effects of sleep therapies in the treatment for epilepsy.

Acknowledgments

This study was supported in part by a research fund from Chosun University in 2011. The authors would like to thank Dr. Madeleine Grigg-Damberger for her thoughtful review of the manuscript.

Disclosures

We acknowledge that all coauthors have been substantively involved in the study and/or the preparation of the manuscript; no undisclosed groups or persons have had a primary role in the study and/or in manuscript preparation; and all coauthors have seen and approved the submitted version of the paper and accept responsibility for its content.

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines. Dr. Foldvary-Schaefer receives grant support from ResMed, a PAP device company. The remaining authors have no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.yebeh.2014.07.005.

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